Arizona Influenza Pandemic Response Plan
Supplement 7: Antiviral Drug Distribution and Use

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I. RATIONALE

Appropriate use of antiviral agents during an influenza pandemic may reduce morbidity and mortality and diminish the overwhelming demands that will be placed on the healthcare system. Antivirals might also be used during the Pandemic Alert Period in limited attempts to contain small disease clusters and potentially slow the spread of novel influenza viruses.

Drugs with activity against influenza viruses ("antivirals") include the M2 ion channel inhibitors or amantadanes [*amantadine* (Symmetrel ®) and *rimantadine* (Flumadine®)] and the neuraminidase inhibitors [*oseltamivir* (Tamiflu ®) and *zanamivir* (Relenza®)]. These drugs have been useful for the management of interpandemic (i.e. seasonal) influenza.

However, a large and uncoordinated demand for antivirals early in a pandemic could rapidly deplete national and local supplies. Planning for optimal use of antiviral stocks is therefore essential. During an influenza pandemic, the Arizona Department of Health Services (ADHS) will need to play a central role in insuring that limited supplies of antivirals will be distributed efficiently to where there is the greatest need and benefit.

II. OVERVIEW

Supplement 7 provides recommendations to state and local partners and to healthcare providers in Arizona on the distribution and use of antiviral drugs for treatment and prophylaxis during an influenza pandemic. These recommendations are up to date as of January 2006, and will be revised as new information is available.

In this document the term "novel strains of influenza" refers to avian or animal influenza strains that can infect humans (like avian influenza virus or swine influenza virus), or new or re-emergent human influenza viruses that cause cases or clusters of human disease. **A pandemic occurs when a novel influenza virus emerges that can infect humans and be efficiently transmitted from person to person.**

The **Interpandemic and Pandemic Alert Period** recommendations focus on 1) preparedness planning for the rapid distribution and use of antiviral drugs, 2) the use of antiviral drugs in the management and containment of cases and clusters of infection with novel or pandemic strains of influenza, and 3) the education of healthcare providers about antiviral use in the management of both seasonal and pandemic influenza.

The **Pandemic Period** recommendations focus on the local use of antiviral drugs in three situations: 1) when pandemic influenza is sporadically reported in the United States (without evidence of spread in the United States), 2) when there is limited transmission of pandemic influenza in the United States, and 3) when there is widespread transmission in the United States.

Throughout the Pandemic Period, education of health care providers will continue. ADHS recommendations for optimal use of limited stocks of antivirals will be updated throughout the course of an influenza pandemic to reflect new epidemiologic data, laboratory results, and the availability of an effective pandemic influenza vaccine.

III. SUMMARY OF PUBLIC HEALTH ROLES AND RESPONSIBILITIES FOR ANTIVIRAL DISTRIBUTION AND USE

Interpandemic and Pandemic Alert Periods

1. Healthcare providers
    a. Learn how to identify influenza-like illnesses
    b. Know procedures for influenza screening and laboratory testing
    c. Know appropriate infection control measures for influenza
    d. Know appropriate antiviral regimens for influenza A and B
2. ADHS and county and tribal health departments
    a. Develop state-based plans for the distribution and use of antivirals during a pandemic (ADHS)
    b. Work with stakeholders to develop a system by which ADHS will assist in brokering antivirals during a pandemic where there is limited supply
    c. Develop state-based plans for requesting antivirals through the Strategic National Stockpile (SNS)
    d. Work with stakeholders to develop a system to monitor interpandemic use of antivirals throughout the state (ADHS and county and tribal health)
    e. Procure a supply of antivirals under the control of ADHS for to use for special populations (ADHS)
    f. Help educate healthcare providers about clinical presentation and control of novel and pandemic influenza (ADHS and county and tribal health)
    g. Give guidance to healthcare providers about using antivirals in the medical management of cases of novel strains of influenza (ADHS and county and tribal health)
    h. Provide or facilitate testing and investigation of suspected novel influenza cases (ADHS and county and tribal health)
    i. Conduct follow-up of suspected novel influenza cases (County health departments)
3. HHS
    a. Develop national guidance on the use of antivirals during both the pandemic alert and pandemic periods
    b. Develop a national stockpile of antiviral drugs for use during a pandemic
    c. Identify priority groups for antiviral drug treatment and prophylaxis
    d. Procure and maintain national supplies of antivirals in the Strategic National Stockpile (SNS)
    e. Maintain a program to test and extend dating of stockpiled antivirals
    f. Develop protocols for monitoring antiviral effectiveness, safety, and resistance during a pandemic
    g. Develop and distribute communication and education materials about antivirals for use by states and other stakeholders

Pandemic Period

- Healthcare providers
    1. Choose antivirals appropriate for circulating influenza strains
    2. Follow recommendations on antiviral use from federal, state, and local health agencies
    3. When antiviral supplies are limited, prescribe antivirals for persons in priority groups where the need and benefit are the greatest
- ADHS and local health departments
    1. Work with healthcare partners to activate plans for distributing and administering antivirals to persons in priority groups (county health departments)
    2. Review and modify as needed recommendations for prioritization of antiviral treatment and prophylaxis (ADHS)
    3. Accelerate training on the appropriate use of antivirals among public health staff and healthcare partners (ADHS and county and tribal health)
    4. Work with CDC to monitor antiviral drug use and effectiveness, to monitor antiviral drug resistance, and to monitor and investigate adverse events associated with antivirals (ADHS)
    5. Work with other governmental agencies and non-governmental organizations to ensure effective public health communications (ADHS and county and tribal health)
- HHS responsibilities
    1. Revise recommendations for treatment and prophylaxis with antivirals for priority groups, if necessary
    2. Provide state, territorial and local health departments and healthcare partners with guidance on reporting specifications for tracking distribution, effectiveness, and safety of antivirals.
    3. Work with WHO and global partners to determine and monitor the drug susceptibilities of the pandemic strain
    4. Provide state, territorial and local health departments and healthcare partners with guidance on reporting specifications for tracking distribution, effectiveness, and safety of antivirals
    5. Provide information to health professionals and the public on issues related to availability and use of antiviral drugs during an influenza pandemic
- Federal responsibilities
    1. Maintain stockpiles of influenza antiviral drugs at the SNS
    2. Distribute antiviral drugs from the SNS to states, cities, and federal agencies as appropriate
    3. Work with states to monitor antiviral drug use and effectiveness, to monitor antiviral drug resistance, and to monitor and investigate adverse events associated with antivirals
    4. Monitor the emergence of antiviral resistance
    5. Issue updated national guidelines for appropriate use of antivirals as the pandemic continues

6. Continue to provide pertinent information to health professionals and the public on drug availability, distribution, administration, side effects, and the rationale for targeted drug use

IV. RECOMMENDATIONS FOR ANTIVIRAL USE IN THE INTERPANDEMIC AND PANDEMIC ALERT PERIODS

A. Use of antivirals in management of seasonal strains of influenza

Influenza epidemics occur every winter in Arizona. Antiviral medicines are a useful adjunct to influenza vaccine for controlling, treating, and preventing influenza (MMWR July 29, 2005 http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm). Current human influenza illness in the United States can be treated and prevented with antivirals.

The M2 ion channel inhibitors (also known as amantadanes) are amantadine (Symmetrel®) and rimantadine (Flumadine®). They have historically been effective for most influenza A strains. The neuraminadase inhibitors oseltamivir (Tamiflu®) or zanamivir (Relenza®) are effective for both influenza A and B. Although many influenza A strains are sensitive to amantadine or rimantadine, the avian influenza A (H5N1) isolates are resistant. At the present time, avian influenza A (H5N1) is usually sensitive to both oseltamivir and zanamivir.

As long as pandemic influenza is not being reported abroad or in the United States, and there is no epidemiologic link to cases of avian influenza, seasonal influenza is unlikely to be caused by a novel influenza virus. Epidemiologic links that should suggest the risk of a novel influenza virus would include:

- A history of travel to areas where there are avian influenza outbreaks
- A history of contact with a person with an unexplained respiratory disease in an area with avian influenza outbreaks
- Contact with patients ill with a known or suspected novel virus
- Contact with sick poultry

See Clinical Guidelines Supplement 5 for more detailed information about epidemiologic criteria for suspecting a novel influenza virus.

Physicians can use antiviral medicines to treat and give prophylaxis against seasonal influenza. Treatment is most effective in reducing the length of illness when given within the first 48 hours of symptoms. Physicians should chose which antiviral medicine to use based on a variety of factors:

- What strain is currently circulating in the community (influenza A or B or both)
- The known sensitivities to antivirals of these circulating strains
- Rapid influenza testing results
- The age of the patient
- Whether the antiviral medicine will be used for treatment or prophylaxis

(See Appendix 3: ADHS Clinician Fact Sheet: Antivirals for Influenza 2005-2006; Appendix 4: ADHS Clinician Fact Sheet: Influenza 2005-2006; and MMWR July 29, 2005 http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm)

The educational components about antivirals of the ADHS' Pandemic Influenza Plan will assist healthcare providers in the appropriate use of antivirals during seasonal influenza. This will allow healthcare providers to be better prepared to use antivirals during pandemic influenza.

B. Use of antivirals in management of cases of novel influenza

In this document the term "novel strains of influenza" is used to refer to avian or animal influenza strains that can infect humans (like avian influenza A [H5N1]) and new or re-emergent human influenza viruses that cause cases or clusters of human disease. Criteria for early detection and identification of novel strains of influenza are discussed in Supplement 1.

Sentinel laboratories throughout Arizona send influenza isolates to Arizona Public Health Laboratory. Influenza A viral isolates are tested to detect hemagglutinins H1, H3, H5, or H7. Recent circulating influenza strains have been H1 and H3. If the isolate were H5 or H7, or if could not be identified, the isolate would be immediately sent to the Centers for Disease Control and Prevention (CDC) for further characterization to exclude a novel influenza virus.

1. Use of antivirals for TREATMENT of suspected avian influenza A (H5N1) or another novel strain of influenza.

A patient with a suspected case of avian influenza A (H5N1) or another novel strain of influenza should be isolated as described in Supplement 4 and treated in accordance with the clinical algorithm for the Pandemic Alert Period provided in Supplement 5.

As of December 2005, a patient with a suspected case of avian influenza A (H5N1) or another novel strain of influenza should be treated with oseltamivir or zanamivir. The antiviral should be administered as early as possible and ideally **within 48 hours after onset of symptoms**.

Neuraminidase inhibitors are preferred because the majority of avian influenza A (H5N1) viruses currently affecting humans are resistant to amantadine and rimantadine. Cross-resistance between zanamivir- and oseltamivir-resistant viruses is variable. Current recommended doses for antiviral treatment are provided in Table 2 and in ADHS' Clinician Fact Sheet on Antivirals for Influenza in Appendix 3. This information will be updated as circumstances warrant.

2. Use of antivirals for PROPHYLAXIS of contacts suspected avian influenza A (H5N1) or another novel strain of influenza.

ADHS and local health departments, in consultation with CDC, will consider whether it is necessary and feasible to trace a patient's close contacts and provide them with postexposure antiviral prophylaxis**.** Close contacts may include family, schoolmates, workmates, healthcare providers, and fellow passengers if the patient has been traveling.

If deemed necessary by public health authorities, these persons may receive post-exposure prophylaxis with oseltamivir, as zanamivir is not currently indicated for prophylaxis.

If the exposure to the novel influenza virus strain occurs during the regular influenza season, the patient's healthcare contacts (who may also care for persons with seasonal influenza) should be **vaccinated against seasonal influenza** to reduce the possible risk of co-infection and reassortment of seasonal and novel strains.

3. Use of antivirals for containment of disease clusters caused by suspected avian influenza A (H5N1) or another novel strain of influenza.

In special circumstances, ADHS could recommend "targeted antiviral prophylaxis" as a community-based measure for containing small clusters of infection with novel strains of influenza (see Supplement 8). This measure would be implemented in small, well-defined settings such as the initial introduction of a virus with pandemic potential into a small community or a military base. However, once a pandemic is underway, such a strategy would not represent an efficient use of limited antiviral supplies.

Because targeted antiviral prophylaxis would require rapid delivery and administration of substantial stocks of antiviral drugs, the feasibility to use antivirals to contain disease clusters caused by a novel strain of influenza will be evaluated at the time based on available antiviral supply and interim updated recommendations on antiviral drug use. These decisions will involve the Vaccine and Antiviral Prioritization Policy Committee (VAPPC) as described below in C-2-b: "Establishing priority groups."

Targeted antiviral prophylaxis would involve investigation of disease clusters, administration of antiviral treatment to persons with confirmed or suspected cases of pandemic influenza, and provision of drug prophylaxis to all persons in the affected community. Targeted antiviral prophylaxis would also require intensive case finding in the affected area as well as effective communication with the affected community.

C. Preparedness planning for use of antivirals during a pandemic

1. National recommendations on use of antivirals during a pandemic

During an influenza pandemic, demand is likely to far outstrip supplies available in stockpiles or through usual channels of distribution. The U.S. Department of Health and Human Services' HHS Pandemic Influenza Plan, November 2005 Part 1, Appendix D, table D-2, page D-21 (http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf) provides a list of priority groups for receiving antiviral treatment or prophylaxis and the rationale for prioritization

During an actual pandemic, these recommendations will be modified, based on the characteristics of the causative virus (e.g., drug susceptibilities, initial geographic distribution, fatality rate, age-specific morbidity and mortality rates) and the effectiveness of implemented strategies.

2. Arizona planning

ADHS is working with the federal government, local health departments, tribal governments, bordering states, and the government of Sonora, Mexico to develop and integrate state-based plans for antiviral needs assessment, procurement, distribution, and targeted use. ADHS will use:

- Interim recommendations developed by the National Vaccine Advisory Committee on priority groups for prophylaxis and treatment (http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf) to assist in calculations for Arizona priority groups
- Strategies outlined in Box 1 for optimizing antiviral use in treatment and prophylaxis.
- Clinical treatment algorithms provided in Clinical Guidance Supplement 5
- Existing ADHS plans for emergency distribution of medical supplies

ADHS has, as part of its Influenza Pandemic Response Plan, procuring antiviral drugs for state and local stockpiles; distributing antivirals to priority groups by healthcare providers and through public health dispensing sites; data collection to monitor drug use, drug-related adverse events, and drug resistance; coordination with bordering jurisdictions; legal preparedness; training; and dissemination of public health information.

This requires coordination and collaboration with healthcare providers who will administer antivirals during a pandemic.

- ADHS will convene state-wide pandemic influenza strategy meetings on the use of antivirals to facilitate local planning and define public- and private-sector roles (e.g., related to rapid administration to priority groups and medical surge capacity)
- ADHS continues to communicate with the medical community throughout the state about national guidelines for treatment and prophylaxis and the appropriate use of antivirals
- ADHS is beginning to identify, and will maintain, contacts with federal agencies, local health departments, tribal governments, bordering states, and the government of Sonora, Mexico for coordinating distribution of antivirals.

a. Procurement

The needs in Arizona for antiviral treatment and prophylaxis during an influenza pandemic will likely not be met by federally supplied antivirals from the SNS stockpile. Therefore, state and local governments, and private institutions need to consider additional ways to obtain antivirals.

Typically, human influenza outbreaks can be prevented and treated with four different antivirals. Influenza A usually can be treated with amantadine (Symmetrel ®) or rimantadine (Flumadine®) or the neuraminadase inhibitors oseltamivir (Tamiflu ®) or zanamivir (Relenza®). Influenza B is only sensitive to neuraminidase inhibitors. Unfortunately, the currently circulating avian influenza strain H5N1 is not sensitive to amantadine or rimantadine. Additionally, on January 16, 2006, CDC announced that the adamantanes were no longer recommended treatments against the human influenza strains circulating in the 2005-2006 influenza season, due to reportedly high rates of resistance (91%). Zanamivir has only been approved for treatment of influenza. Therefore, oseltamivir is the only antiviral drug that would be available for *both prophylaxis and treatment*.

ADHS has estimated the quantity of antiviral drugs that would be needed in Arizona (see Appendix 1) based on the U.S. Department of Health and Human Services' Pandemic Influenza Plan, November 2005 (http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf). The cumulative amount to provide oseltamivir for all 11 of these priority groups would require 2,615,500 treatment courses, or 26,155,000 doses of oseltamivir.

Procurement of State Stockpile

Due to space constraints, management logistics, and challenges with rotating stock, ADHS will only be able to maintain a limited stockpile of antiviral medicines. ADHS has identified $1,000,000 to procure oseltamivir. Potential recipients of the ADHS stockpile of oseltamivir will include people who have an urgent and pressing need for antiviral therapy but are not covered by existing distribution processes, such as public health workers, hard to reach populations, and institutional outbreaks.

Management of State Antiviral Stockpile

ADHS is the responsible authority for coordinating and managing the Arizona antiviral stockpile. Stockpiled antiviral inventory will be managed to prevent expiration of purchased antivirals. The ADHS stockpile may be managed under:

- vendor-managed inventory (VMI),
- direct ADHS management, where the stockpile would be stored, rotated, and from where it would be distributed
- agreement with specific hospitals that they would rotate ADHS' supply into their own pharmaceutical supply.

Arizona will increase the supply of antivirals for pandemic influenza in Arizona by 1) encouraging healthcare facilities to consider their own institutional stockpiles or vendor-managed inventories, 2) explore how to make arrangements with local private-sector distributors for emergency purchase of antiviral drugs, and 3) when needed, requesting antivirals from the Strategic National Stockpile (SNS).

ADHS' office of HIV/AIDS Services has developed an infrastructure in order to provide HIV-related medicines for patients throughout the state who are participating in the Arizona Drug Assistance Program (ADAP). As of April 1, 2006, all HIV medicines will be provided and distributed by a large outpatient pharmacy chain. ADHS will explore ways to utilize this infrastructure to assist in distributing antivirals to community pharmacies.

b. Establishing priority groups

In situations where there are limited supplies of antivirals for influenza, the medicine should go to people who have the greatest need and are most likely to benefit from it.
The highest priority should be **treatment** of **high-risk individuals** who are **hospitalized** due to pandemic influenza illness.
The next priorities would be 1) **prophylaxis** of health care workers (HCW) with direct patient contact and emergency medical service (EMS) providers, and 2) **treatment** of pandemic health responders (public health, vaccinators, vaccine and antiviral manufacturers), public safety (police, fire, corrections), and government decision-makers.
Only when there is adequate antiviral medicine should there be able to be **treatment** of low-risk outpatients and **prophylaxis** of high-risk outpatients and other high-risk health care workers.

In the interpandemic and pandemic alert periods, ADHS will establish a Vaccine and Antiviral Prioritization Policy Committee (VAPPC) composed of

- Representative(s) from the Governor's office
- State Epidemiologist
- State physician(s)
- ADHS influenza epidemiologist
- Office of Infectious Disease Services office chief
- ADHS administrator(s)
- Arizona Immunization Program Office (AIPO) representative
- Arizona Local Health Officers Association representative
- Arizona Medical Association representative
- Hospital Association representative
- Emergency Medical Service representative
- Arizona Pharmacy Alliance representative
- Long-term care representative

The VAPPC will define how these priority groups will apply on a local level, and will define who should be included in the groups of public safety workers, essential service providers, and key governmental decision makers.

During an influenza pandemic, the VAPPC will modify these priority groups as needed based on the availability of antiviral medicines, the characteristics of the causative virus (e.g., drug susceptibilities, initial geographic distribution, fatality rate, age-specific morbidity and mortality rates) and the effectiveness of implemented strategies.

The VAPPC will provide the rationale for establishing the priority groups so that the reasons for prioritization can be communicated to the community.

Appendix 1 provides estimates for treatment and prophylaxis of priority groups based on the 11 priority groups in the HHS Pandemic Influenza Plan, November 2005 table D-2, page D-21, found at http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf. One underlying assumption is that 25% of the U.S. population would become ill with influenza. The cumulative amount to provide oseltamivir for all 11 of these priority groups in Arizona would require 2,615,500 treatment courses, or 26,155,000 doses of oseltamivir. These initial calculations can help the VAPPC to estimate the size of the various priority groups in Arizona.

c. Distributing and dispensing antivirals to priority groups

Deciding how, where, and when to distribute

Distribution of antivirals will depend on the amounts of antivirals available in the state, the priority groups that are to be targeted (as per the VAPPC), and the locations of greatest need. In order to equitably and effectively distribute antivirals to priority groups during an influenza pandemic, ADHS will need to know the location and amount of antivirals throughout the state, and be able to rapidly direct their flow to the appropriate priority groups.

During the interpandemic and pandemic alert periods, ADHS will:

- Work with stakeholders to develop a system to assess and track antiviral stocks at the state and local level (both in inpatient and outpatient settings) to allow for tracking during a pandemic.
- Constitute and exercise the VAPPC
- Work with local health departments to plan for and to exercise the distribution of antiviral medicines based on priorities and needs.
- Establish the legal authority to have standing orders for antivirals both at the state and local health department level
- Explore how to implement standing orders if they are needed for treatment of certain priority groups (e.g. hospitalized patients and healthcare workers)
- Review and update pre-existing plans for the transport, receipt, storage, security, tracking, and delivery of:
    - Antiviral stocks for use in treatment to hospitals, clinics, nursing homes, alternate care facilities, and other healthcare institutions.
    - Antiviral stocks for use in post-exposure prophylaxis (e.g., for direct contacts of infected patients)
    - Antiviral stocks for use in prophylaxis even when there is no known direct pandemic influenza exposure (e.g. pandemic health responders, public safety workers, government decision-makers, and pandemic societal responders)
- Explore how to implement standing orders for antivirals for high priority groups (e.g. hospitalized patients, health care workers, etc.)
- Develop a system to obtain antivirals for treatment of pandemic influenza, or prophylaxis of a close contact of someone with pandemic influenza, where lack of financial resources prevents the individual from purchasing available antivirals.

During an influenza pandemic, ADHS will:

- Handle requests for antivirals through an incident command system (ICS).
    - The providers would request antivirals through their local health department [or county Emergency Operating Center (EOC)] and these requests would be sent on to ADHS [or the Arizona state EOC].
- Be guided by the VAPPC's recommendations about priority groups
- Request and handle SNS antiviral supplies according to the ADHS SNS Plan for Receipt, Store, and Stage (RSS)

ADHS Brokering of Antiviral Supply

According to Arizona Revised Statutes 36-787 [http://www.azleg.state.az.us/FormatDocument.asp?inDoc=/ars/36/00787.htm&Title=36&DocType=ARS], during a state of emergency in which there is a pandemic disease that poses a substantial risk of a significant number of human fatalities, the Governor, in consultation with the director of the Department of Health Services, may issue orders that ration medicine and vaccines, and provide for procurement of medicines and vaccines.
Under these circumstances, ADHS will take the lead to direct the prioritization of limited antiviral supplies during an influenza pandemic.

ADHS does not have the capacity to purchase, store, rotate, and distribute the estimated 2,615,500 treatment doses of oseltamivir that would be needed in Arizona if all 11 priority groups were to receive medication (see Appendix 1).

Therefore, ADHS would need to use the current system of antiviral distribution in order to get antiviral medicines to patients during an influenza pandemic. In the interpandemic and pandemic alert period, ADHS will assist providers in overcoming antiviral shortages by informing them of ways to obtain antivirals. Hospitals will be encouraged and to prepare and maintain their own antiviral stockpile.

During the pandemic period, if there are inadequate supplies of antivirals, ADHS will work directly with the manufacturer and the pharmaceutical distributors, in order to direct and broker the flow of medicines. Priority distribution will go to the sites of greatest need that service the **highest priority groups** according to the priorities outlined in C-2-b.

The Arizona Immunization Program Office (AIPO) is experienced in the brokering of influenza vaccine during shortages. However, early in an influenza pandemic, vaccine will not be widely available, and antivirals will be the pharmaceutical most in need of brokering. Therefore, the AIPO will take the lead at ADHS for brokering antivirals

When the supply of antivirals in Arizona during an influenza outbreak is insufficient to provide for the needs of the citizens, the Director of Arizona Department of Health Services will make an emergency request for federal assets in the SNS. HHS and CDC officials will make the decision whether to deploy federal assets to Arizona. Federal supplies of antivirals will be delivered to

Arizona's Receipt, Storage and Staging (RSS) site. ADHS SNS coordinators will provide logistical guidance on the receipt and distribution of federal assets to priority groups.

Critical Stakeholder's Committee

In order for ADHS to effectively broker antiviral distribution in Arizona during pandemic influenza, there will need to be a broad consensus among stakeholders as to how this best can be accomplished. ADHS will form a Critical Stakeholders' Committee (CSC) to discuss prioritization and implementation of ADHS antiviral plan. Potential stakeholders include:

- Roche (oseltamivir manufacturer)
- Glaxo Wellcome (zanamivir manufacterer)
- Pharmaceutical distributors
- Arizona Board of Pharmacists
- Arizona Medical Association
- Arizona Osteopathic Medical Association
- Arizona Chapter of the American Academy of Pediatrics
- Arizona Hospital Association
- Major local pharmacy chains
- AHCCCS plans
- Large insurance companies
- IHS hospitals
- Tribal health
- ADHS Border Health Office
- County health departments
- Long-term care representative

Topics for discussion with stakeholders will include 1) coordination between manufacturer, distributors, pharmacies, health care providers and ADHS; 2) proposed situations where ADHS would begin actual brokering and prioritization of antivirals; 3) plans on how and when to institute prioritization; 4) restrictions on when physicians can write prescriptions for oseltamivir;

Distribution based on electronic monitoring of supply

ADHS does not have information on the amount and type of antivirals currently used in Arizona. Such information is regarded as proprietary. However, in the United States in 2003-2004, there were 1,524,687 treatments of oseltamivir given (www.iom.edu/Object.File/Master/21/608/0.pdf slide #9). Since Arizona's population is approximately 2% of the United States, a proportional number of oseltamivir treatments would be 30,500.

In order for ADHS to effectively and equitably distribute a limited amount of antivirals, it will be essential to know where, when, by whom, and how much antiviral medicine is needed and/or is being used. That information is not currently available in Arizona. However, ADHS has established an electronic system with pharmacies for syndromic surveillance to watch sales of over the counter medicines. A similar system could be established with antiviral medicines.

ADHS will work with the Critical Stakeholder Committee (CSC) and meet with pharmacy and pharmaceutical representatives to develop a system by which ADHS is informed of the amount and location of antiviral medicines in the state.

d. Monitoring and data collection

To ensure optimal use of antiviral drugs during an influenza pandemic, ADHS will work with federal officials and healthcare partners to collect data on 1) distribution of state or federal supplies of antiviral drugs, 2) occurrence of adverse events following administration of antiviral drugs, 3) effectiveness of treatment and prophylaxis, and 4) development of drug resistance.

1) **Distribution.** ADHS will work with its critical stakeholders through the Critical Stakeholder Committee (CSC) to a system by which ADHS is informed of the amount and location of antiviral medicines in the state. ADHS will establish a Vaccine and Antiviral Prioritization Policy Committee (VAPPC) to give guidance on priority groups for antivirals. The state EOC will keep track of drug distribution and use. The VAPPC will assess whether drugs are being effectively targeted to priority groups and whether distribution is equitable within those groups (e.g., among racial and ethnic minorities and persons of different socioeconomic levels).
2) **Antiviral use and effectiveness.** Studies to evaluate the effectiveness of antiviral drug use during a pandemic will be conducted by federal agencies in collaboration with ADHS and other partners. The effectiveness of antiviral therapy and prophylaxis will be assessed by comparing rates of severe influenza-related illness and death among treated and untreated persons and among persons who did and did not receive prophylaxis. Analyses of antiviral drug effectiveness should take into account characteristics that will vary among individuals and those that may vary over time, such as diagnostic practices, length of time to initiate therapy, and changes in the pandemic virus.
3) **Adverse events.** Serious adverse events associated with the use of antiviral drugs for prophylaxis and treatment of influenza should be reported to FDA, using the MedWatch monitoring program. During an influenza pandemic, ADHS will provide protocols and information to healthcare providers and encourage hospitals to download MedWatch forms (available at http://www.fda.gov/medwatch) for distribution to patients, so that adverse events reported to MedWatch can be collated and analyzed by FDA's Adverse Events Reporting System (AERS).
4) **Antiviral drug resistance.** ADHS will work with CDC to assist in monitoring the development of resistance to antivirals. ADHS will encourage clinicians to obtain specimens from patients who develop severe disease while receiving treatment or prophylaxis. ADHS will provide influenza specimens to CDC on a periodic basis, usually after testing them by RT-PCR, viral culture, or rapid diagnostic testing to confirm the presence of strains of influenza A. CDC will test the drug susceptibilities of viruses isolated from different age groups and geographic groups over the course of the pandemic (see Antiviral Effectiveness above). Changes in antiviral resistance patterns will influence changes in recommendations for treatment and prophylaxis

e. Coordination with bordering jurisdictions

ADHS will review and coordinate antiviral drug distribution plans with health authorities in bordering jurisdictions, including:

- Arizona Counties
- Tribal governments
- Mexico, specifically the state of Sonora

- Surrounding states

During an influenza pandemic, ADHS will share details regarding their distribution of antivirals with these jurisdictions to monitor antiviral needs and optimize targeting of antiviral use.

Due to Arizona's international border, additional planning will be needed with Mexico, since pandemic influenza will not stop at the border with Mexico. If Sonora, Mexico does not have adequate amounts of vaccines and antivirals, people will be coming to the United States for further evaluation and treatment. ADHS will meet with representatives of Sonora, Mexico to share information about pandemic influenza planning as it regards such things as diagnostic supplies, antiviral supplies, provider education, and coordination of pandemic planning. In addition, ADHS will prepare Spanish versions of ADHS messages for the Spanish-speaking public.

f. Legal preparedness

According to Arizona Revised Statutes 36-787, during a state of emergency in which there is a pandemic disease that poses a substantial risk of a significant number of human fatalities, the Governor, in consultation with the director of the Department of Health Services, may issue orders that ration medicine and vaccines, and provide for procurement of medicines and vaccines. [http://www.azleg.state.az.us/FormatDocument.asp?inDoc=/ars/36/00787.htm&Title=36&DocType=ARS]. Under these circumstances, ADHS will take the lead to direct the prioritization of limited antiviral supplies during an influenza pandemic.

During pandemic influenza, there may be a need for the ADHS medical director or local health departments to issue a blanket prescription for dispensing of antivirals. The state medical director would need the authority to do so in a way that is consistent with Arizona's prescription laws.

A problem with blanket prescriptions is that as per ARS 32-1401, 27 (ss), it is unprofessional conduct for a physician to prescribe or dispense a prescription medication to a person without first conducting a physical examination of that person or having previously established a doctor-patient relationship.

However, close contacts of patients with confirmed or suspected pandemic influenza should be able to receive appropriate prophylaxis without undue waiting. Currently, in nonemergency situations, hospitals and treating physicians usually refer patients to local health departments or primary care physicians for prophylactic medications. In a pandemic situation, this would cause undue delay in light of the short incubation period of influenza (1-3 days).

Hospitals and physicians need to have the resources, the authority, and legal protection in order to rapidly provide antiviral prophylaxis to close contacts of confirmed or suspected cases of pandemic influenza.

In addition, there needs to be clarification as to whether adverse side effects of antivirals when taken for prophylaxis by essential workers would be covered by worker's compensation insurance.

ADHS will investigate:

- Ways to give health departments and physicians the authority to issue a blanket prescription for dispensing antivirals to contacts as a public health measure in a way that is consistent with state prescription laws.
- How worker's compensation laws apply to health care workers and other essential workers who take antivirals for prophylaxis.
- Whether a state or county employee would be covered for malpractice or tort claims coverage under state law if they administer an antiviral medication in the course of his/her official duties.
- What legal authority is in place, or needs to be put in place, to facilitate implementation of plans for the ADHS medical director or local health departments to issue a blanket prescription for dispensing of antivirals in a way that is consistent with Arizona's prescription laws.

g. Training

ADHS will work with local health departments, tribal governments, bordering states, and the government of Sonora, Mexico to enhance training and education efforts related to use of antiviral drugs during a pandemic.

ADHS has developed concise information sheets for healthcare providers called Clinician Fact Sheets that give clinically pertinent information about use of antiviral medicines and influenza. (See Appendices 3 & 4). These Clinician Fact Sheets are available on ADHS' influenza website. ADHS will also develop Clinician Fact Sheets for healthcare providers for identifying, diagnosing, and managing pandemic influenza, and post it on the ADHS website.

ADHS physicians, nurses, and epidemiologists will participate in statewide lectures to inform healthcare providers about pandemic influenza and appropriate antiviral use.

It is essential that those who will be involved in prioritizing and distributing antivirals understand their roles and responsibilities. ADHS will conduct exercises with local health departments to plan for and to exercise the distribution of antiviral medicines based on priorities and needs. ADHS will involve its Vaccine and Antiviral Prioritization Policy Committee (VAPPC) and its Critical Stakeholders' Committee (CSC) in these exercises.

h. Public health information

ADHS will work with county health departments, tribal governments, bordering states, and the government of Sonora, Mexico to develop and implement plans to educate the public, the medical community, and other stakeholders about:

- Role of antivirals in responding to pandemic influenza
- Need to prioritize use of limited antiviral supplies for treatment and prophylaxis
- Rationale for the priority groups identified in the interim recommendations
- Importance of appropriate use (i.e., using the drugs as prescribed and for the full number of days recommended) to minimize the development of drug resistance

Pandemic influenza information will also be provided in Spanish.

i. Contingency planning for Investigational New Drug (IND) use

Unlicensed antiviral drugs may be available under FDA's Investigational New Drug (IND) provisions during an influenza pandemic. IND provisions require strict inventory control and record keeping, completion of a signed consent form from each person who receives the medication, and mandatory reporting of specified types of adverse events. IND provisions also require approval of the protocol and consent form by an Institutional Review Board (IRB). These requirements are extremely time consuming.

FDA regulations permit the use of a national or "central" IRB for IND medications, and would likely be used in such a situation. A treatment IND is one IND mechanism that FDA has available for use and is especially suited for large-scale use of investigational products. http://www.access.gpo.gov/nara/cfr/waisidx_99/21cfr_99.html

As an alternative to IND use of an unapproved antiviral drug, HHS may utilize the drug product under Emergency Use Authorization procedures as described in the FDA draft Guidance "Emergency Use Authorization of Medical Products" http://www.fda.gov/cber/gdlns/emeruse.pdf

In order for state and local health departments to be able to help to distribute antiviral drugs under IND provisions, there needs to be funding for nurses, physicians, and pharmacists to provide the necessary services. ADHS will investigate available funding sources and will decide on the feasibility of providing antivirals under IND provisions based on the availability of funding sources and personnel.

V. Recommendations for Antiviral Use in the Pandemic Period

ADHS will update interim recommendations for use of antivirals throughout the course of an influenza pandemic to reflect current epidemiologic and laboratory data. Interim recommendations may also be updated as an effective influenza vaccine becomes available.

A. When pandemic influenza is reported abroad, or sporadic pandemic influenza cases are reported in the United States, without evidence of spread

If an influenza pandemic has begun in other countries, ADHS will work with the federal government, county health departments, tribal governments, bordering states, and the government of Sonora, Mexico to:

- Use antiviral drugs in the management of persons infected with novel strains of influenza and their contacts.
- Work with healthcare partners to provide antiviral prophylaxis to persons at highest risk for pandemic influenza. Examples of such persons include:
    - Public health workers who investigate suspected cases of pandemic influenza
    - Healthcare workers in emergency departments, intensive care units, and, dialysis centers
    - Paramedics and Emergency Medical Technicians
- Meet with local partners and stakeholders to review the state-based antiviral drug distribution plan. As part of this effort, state and local partners will:
    - Modify the distribution plan to take into account
        - Updated federal recommendations on target groups
        - Updated information on projected supplies of antiviral drugs.
    - Notify the medical community about the status of the plan and the availability of antiviral drugs.
    - Disseminate public health guidelines that encourage drug-use practices to minimize the development of drug resistance.
    - Provide the public with information on interim recommendations and their rationale
    - Work with federal partners to monitor the safety and effectiveness of drugs and ensure that available antivirals are used in accordance with federal and local recommendations.

B. When there is limited transmission of pandemic influenza in the United States

When there is limited transmission of pandemic influenza in the United States, ADHS will work with county health departments, tribal governments, bordering states, and the government of Sonora, Mexico to:

- Activate state-based plans for targeting antiviral drugs to priority groups for prophylaxis and treatment.
- Request antiviral drugs, as needed, from previously identified including the SNS.
- Continue to educate healthcare partners to ensure appropriate use of antivirals in the medical management of early cases and contacts.
- Assist hospitals in implementing procedures for early detection and treatment of influenza in healthcare workers (see Supplement 3).
- Work with federal partners to begin monitoring the safety and effectiveness of drugs and ensure that available antivirals are used in accordance with federal and local recommendations.

C. When there is widespread transmission of pandemic influenza in the United States

- When pandemic influenza has become widespread, the goals of antiviral use will be to 1) treat those at highest risk of severe illness and death, and 2) to preserve the delivery of healthcare and other essential critical services through early treatment and limited prophylaxis.
- After a vaccine becomes available, antiviral drugs will continue to be used to protect persons who have an inadequate vaccine response (e.g., the elderly and those with underlying immunosuppressive disease) as well as persons with contraindications to vaccination, such as anaphylactic hypersensitivity to eggs or other vaccine components.
- Until the pandemic has waned, ADHS will continue to work with federal and healthcare partners to monitor the safety and effectiveness of antivirals and to encourage appropriate drug use practices that help minimize the development of drug resistance.

Box 1. Strategies for Antiviral Use in Pandemic Influenza Treatment and Prophylaxis

The goals of vaccine and antiviral use during an influenza pandemic are to limit mortality and morbidity, minimize social disruption, and reduce economic impact. Because a pandemic vaccine is unlikely to be available during the first 4 to 6 months of the pandemic, appropriate use of antivirals may play an important role in achieving these goals.

A. Treatment

1. Planning considerations

- The effectiveness of antivirals against a new pandemic influenza virus cannot be predicted.
- Early treatment may reduce the risk of hospitalization by ~50%, although there are no data on the effectiveness of neuraminidase inhibitors in preventing either serious morbidity or mortality (MMWR July 29, 2005 http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).
- Antiviral agents used against seasonal influenza show efficacy in clinical trials when treatment is started within 48 hours of the onset of symptoms. Assuming that antivirals have a similar level of effectiveness against pandemic influenza, it will be essential to have rapid diagnosis, distribution, and administration of antivirals during a pandemic.
- Early treatment is a more efficient use of antivirals than widespread prophylaxis. Because prophylaxis for approximately 6 weeks would require at least four times the number of doses as a 5-day treatment course per individual, huge antiviral stockpiles would be required to permit prophylaxis of more than a small proportion of the U.S. population.
- Most influenza A (H5N1) viruses currently in circulation in southeast Asia are resistant to the M2 ion channel inhibitors (amantadine and rimantadine). Strains that may evolve from these viruses are likely to be resistant to this class of antivirals.
- The emergence of drug resistant strains is less likely during treatment with neuraminidase inhibitors (oseltamivir and zanamivir) than with M2 ion channel inhibitors (amantadine and rimantadine). Neuraminidase inhibitors may also have a lower incidence of severe side (MMWR July 29, 2005 http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).

Reserve oseltamivir and zanamivir for treatment whenever possible. Because supplies of oseltamivir and zanamivir are expected to be limited, early depletion of oseltamivir and widespread use of M2 ion channel inhibitors could lead to increased rates of side effects and drug resistance.

Box 1. Strategies for Antiviral Use in Pandemic Influenza Treatment and Prophylaxis – cont.

2. Treatment Strategies

Optimal use of limited stocks of antiviral drugs will vary depending on the phase of the pandemic. The following is interim guidance that will be updated as more information becomes available.

At all stages of a pandemic:

- Target antiviral therapy to influenza patients admitted to a hospital who present within 48 hours of symptom onset.
- Test to detect the emergence of drug-resistant variants of a pandemic influenza strain (e.g., obtaining specimens from persons who develop influenza while on prophylaxis or who progress to severe disease despite treatment).
- Modify priority groups for treatment based on up-to-date information (e.g. drug supplies, drug susceptibilities, geographic distribution, fatality rate, age-specific morbidity and mortality rates, and the effectiveness of implemented strategies).
- Monitor availability of antivirals. When appropriate, recommend changes in priority groups for receiving antivirals
- Purchase antivirals as needed as they become available if not provided by the federal government.
- Distribute antivirals as they become available
- Use an electronic management system for antiviral inventory tracking. ADHS and the Division of Strategic National Stockpile are both working to develop such a management system.

During the earliest stages of a pandemic in the United States:

- Antiviral treatment decisions should be made on laboratory results. A positive rapid antigen test for influenza A would be sufficient grounds for initiating treatment, with a confirmatory, definitive laboratory test required for continuation of treatment (e.g. viral isolate or RT-PCR).
- Negative results of influenza testing would permit stopping antiviral treatment, given the overall low rate of infection in a particular community.
- Target use of antivirals to contain small, well-defined pandemic disease clusters, to possibly delay or reduce the spread to other communities (see Supplement 8**)**.

When there is increasing disease activity in the United States:

- Treatment decisions will be based on:
    - Laboratory-confirmed identification of the pandemic subtype (e.g. by viral isolation and subtyping, or RT-PCR), *or*
    - Detection of influenza A by rapid antigen test, *or*
    - Epidemiologic and clinical characteristics.
- Initiation of antiviral treatment should be on a clinical basis (i.e. before results from viral isolation, IFA, RT-PCR assays, or rapid antigen tests become available) since early treatment is more likely to be effective.

Box 1. Strategies for Antiviral Use in Pandemic Influenza Treatment and Prophylaxis – cont.

Once infection becomes more common, negative rapid antigen test results are more likely to represent false negatives; therefore, treatment should continue while awaiting results from confirmatory testing.

When the pandemic is widespread in the United States:

- Antiviral treatment decisions will be made on clinical features and epidemiologic risk factors, taking into account updated knowledge of the epidemiology of the pandemic virus.

As the pandemic progresses, recommendations for antiviral treatment will be revised as new information is obtained about the pandemic strain.

B. Prophylaxis

1. Planning considerations for prophylaxis

- Primary constraints on the use of antivirals for prophylaxis will be:
  - Limited supplies
  - Increasing risk of side effects with prolonged use
  - Potential emergence of drug-resistant variants of the pandemic strain.
- The need for antiviral prophylaxis may decrease once an effective pandemic influenza vaccine becomes available for use among healthcare workers and other groups.
- Post-exposure prophylaxis might be useful in attempts to control small, well-defined disease clusters (institutional outbreaks or household introductions). The potential use of targeted prophylaxis to contain disease clusters is discussed in **Supplement 8.**
- The number of persons who receive **prophylaxis** with oseltamivir should be **minimized**, primarily to extend supplies available to treat persons at highest risk of serious morbidity and mortality. If sufficient antiviral supplies are available, prophylaxis should be used only during peak periods of viral circulation to protect small groups of front-line healthcare workers and other providers of essential community services prior to availability of vaccine.
- If a pandemic virus is susceptible to M2 ion channel inhibitors, amantadine and rimantadine can be used for prophylaxis, although drug resistance may emerge quickly.
- Where supplies allow, rimantadine is preferred over amantadine, because it is associated with a lower incidence of serious side effects. Strains that are resistant to amantadine are likely resistant to rimantadine.
- Prophylaxis with amantadine or rimandatine decreased the risk of influenza illness during the 1968 pandemic and the 1977 reappearance of H1N1 viruses.*
- A study of post-exposure prophylaxis using amantadine—conducted during the 1968 pandemic—demonstrated little effectiveness, possibly due to rapid development of resistance.*
- Oseltamivir has >70% efficacy as prophylaxis against laboratory-confirmed febrile influenza illness during interpandemic periods in unimmunized adults.*

*See MMWR July 29, 2005 http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf

Box 1. Strategies for Antiviral Use in Pandemic Influenza Treatment and Prophylaxis – cont.

2. Strategies for prophylaxis

Strategies for effective use of antiviral prophylaxis during a pandemic include:

- **Targeting prophylaxis to priority groups throughout the first wave of the pandemic**. . (See **Appendix 1,** and U.S. Department of Health and Human Services' HHS Pandemic Influenza Plan, November 2005, Appendix D: NVAC/ACIP recommendations for prioritization of pandemic influenza vaccine and NVAC recommendations on pandemic antiviral drug use, table D-2, page D-21, http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf. Data from 20th century influenza pandemics suggest that the first wave of these pandemics lasted approximately 4 to 8 weeks in a community
- **Using post-exposure prophylaxis** (generally for 10 days) to:
    - Control small, well-defined disease clusters, such as outbreaks in nursing homes or other institutions, to delay or reduce transmission to other communities.
    - Protect individuals with a known recent exposure to a pandemic virus (e.g., household contacts of pandemic influenza patients).
- **Modify priority groups for prophylaxis based on up-to-date information** (e.g. drug supplies, drug susceptibilities, geographic distribution, fatality rate, age-specific morbidity and mortality rates, the effectiveness of implemented strategies, and when a vaccine becomes available).
- **Consider post-exposure prophylaxis to protect key personnel** (when a vaccine becomes available) during the period between vaccination and the development of immunity.

C. Strategies for Combined Treatment and Prophylaxis

During the Pandemic Alert Period, combined antiviral treatment for ill persons and targeted post-exposure prophylaxis of contacts would be considered in attempts to contain small disease clusters (e.g., institutional outbreaks or household introductions as described in **Supplement 8.**

The administration of oseltamivir does not interfere with the development of antibodies to influenza viruses after administration of trivalent inactivated influenza vaccine. Therefore, persons receiving prophylaxis can continue to receive oseltamivir during the period between vaccination and the development of immunity. Whether oseltamivir can interfere with the immune response elicited by a live-attenuated pandemic vaccine is unknown.

Box 1. Strategies for Antiviral Use in Pandemic Influenza Treatment and Prophylaxis – cont.

D. Pediatric Use

None of the available influenza antivirals are currently FDA approved for use among children aged <1 year. In particular, the safety and efficacy of oseltamivir have not been studied in children aged <1 year for either treatment or prophylaxis of influenza (see oseltamivir package insert). The decision by an individual physician to treat children aged <1 year in an emergency setting on an off-label basis with an antiviral must be made on a case-by-case basis with full consideration of the potential risks and benefits.

Oseltamivir is available as an oral suspension for use in children. However, this formulation of oseltamivir may not be available in sufficient supply during a pandemic to treat all pediatric patients. If physicians use 75 mg oseltamivir capsules to deliver a partial, pediatric dose to children, they should know that there are insufficient data on palatability, stability, and dosing consistency to predict the safety or effectiveness of such a use.

Box 2. Federal Supplies of Antiviral Drugs in the Strategic National Stockpile

During an influenza pandemic, a decision to deploy federal assets from the Strategic National Stockpile (SNS) will be made by HHS. As of October 2005, the SNS (http://www.bt.cdc.gov/stockpile/) contained 2.26 million treatment regimens of oseltamivir (capsules and suspension), 5 million treatment regimens of rimantadine (tablets and syrup), and 84,000 treatment regimens of zanamivir. Two million additional oseltamivir courses will be delivered to the SNS by November 2005 and additional purchases of antivirals are pending. The details of the HHS approach for allocation and distribution of SNS assets during an influenza pandemic are currently under consideration. ADHS will work with federal the federal government, local health departments, tribal governments, bordering states, and Sonora, Mexico to:

- Develop plans to allot antivirals to healthcare facilities, assuming that distribution of limited supplies of antivirals will initially be targeted to patients hospitalized with pandemic influenza and for treatment or prophylaxis of essential healthcare workers.
- Develop a system that would allow for standing orders for the prescription of antivirals, particularly for use in healthcare workers.
- Work with occupational health clinics in hospitals and other healthcare organizations on plans for delivery of antivirals to healthcare workers.
- Instruct healthcare providers **not** to prescribe oseltamivir to individuals for prophylaxis against pandemic influenza, and counsel individuals **not** to stockpile oseltamivir in homes. At the present time, antivirals are needed to treat and give prophylaxis to the highest priority groups for the current seasonal influenza. Inappropriate use and stockpiling of oseltamivir will take away necessary resources from those who have the highest priority.

Table 1. Characteristics of Anti-Influenza Antiviral Drugs

	Inhibits	Acts on	Administration	Common Side Effects
Amantadine	M2 ion channel	Influenza A	Oral	CNS, GI
Rimantadine	M2 ion channel	Influenza A	Oral	CNS, GI (less often than amantadine)
Oseltamivir	Neuraminidase	Influenza A and B	Oral	GI
Zanamivir	Neuraminidase	Influenza A and B	Inhaler	Bronchospasm

These agents differ in mechanisms of action, pharmokinetics, FDA-approved indications, dosages, cost, and potential for emergence of drug resistance (see July 2005 recommendations of the AHIC (http://www.cdc.gov/mmwr/PDF/rr/rr5408.pdf).
The neuraminidase inhibitors and rimantadine are superior to amantadine with regard to the frequency of serious side effects.
The use of M2 ion channel inhibitor, particularly for treatment, is likely to lead to the emergence and spread of drug-resistant influenza viruses.

Source of Table 1: http://www.hhs.gov/pandemicflu/plan/10

Table 2. Recommended Daily Dosage of Antivirals for Treatment and Prophylaxis

(From *Prevention and Control of Influenza, Recommendations of the Advisory Committee on Immunization Practices [ACIP], MMWR July29, 2005*)

	Age Groups (years)				
Antiviral Agent	**1–6**	**7–9**	**10–12**	**13–64**	**≥65**
Amantadine[a]					
Treatment, influenza A	5mg/kg body weight/day up to 150 mg in two divided doses [b]	5mg/kg body weight /day up to 150 mg in two divided doses [b]	100 mg twice daily [c]	100 mg twice daily [c]	≤100 mg/day
Prophylaxis, influenza A	5mg/kg body weight /day up to 150 mg in two divided doses [b]	5mg/kg body weight /day up to 150 mg in two divided doses [b]	100 mg twice daily [c]	100 mg twice daily [c]	≤100 mg/day
Rimantadine [d]					
Treatment,[e] influenza A	NA[f]	NA	NA	100 mg twice daily [c,g]	100 mg/day
Prophylaxis, influenza A	5m/kg body weight /day up to 150 mg in two divided doses [b]	5mg/kg body weight /day up to 150 mg in two divided doses [b]	100 mg twice daily [c]	100 mg twice daily [c]	100 mg/day [h]
Zanamivir[i,j]					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment,[k] influenza A and B	dose varies by child's weight [l]	dose varies by child's weight [l]	dose varies by child's weight [l]	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

[a] The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 ml/min/1.73m2 .

[b] 5 mg/kg body weight of amantadine or rimantadine syrup = 1 tsp/2.2 lbs.
[c] Children aged ≥10 years who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg body weight /day.
[d] A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.
[e] Approved by FDA only for treatment among adults.
[f] Not applicable.
[g] Rimantadine is approved by FDA for treatment among adults. However, certain experts in the management of influenza consider it appropriate for treatment among children. (See American Academy of Pediatrics, 2003 Red Book.)
[h] Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years if they experience possible side effects when taking 200 mg/day.
[i] Zanamivir administered via inhalation using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of the correct use of the device.
[j] Zanamivir is not approved for prophylaxis.
[k] A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.
[l] The dose recommendation for children who weigh ≤15 kg is 30 mg twice a day. For children who weigh >15 to 23 kg, the dose is 45 mg twice a day. For children who weigh >23 to 40 kg, the dose is 60 mg twice a day. And for children who weigh >40 kg, the dose is 75 mg twice a day.

Source of table 2: http://www.hhs.gov/pandemicflu/plan/10

Appendix 1.

Arizona's Priority Groups for Antiviral Use during an Influenza Pandemic

Estimation of the Number of Treatment Courses Required in Arizona for Select Priority Groups

	Priority Group	Strategy	Estimated Population		C.F.	Number of Treatment Courses (10 pills/course)		Rationale
			US (millions)	AZ		Target group	Cumulative courses	
1	Patients admitted to hospital	Treat	10.0	200,000	75%	150,000	150,000	Treat those seriously ill and most likely to die
2	HCWs with direct patient care and EMS	Treat	9.2	184,000	25%	46,000	196,000	HCWs needed for medical care
3	Highest risk outpatients: Pregnant women; immuno-compromised	Treat	2.5	50,000	25%	12,500	208,500	Highest risk of hospitalization and death; hard to protect immuno-compromised by vaccine
4	Pandemic health responders, Public Safety, Government decision-makers	Treat	3.3	66,000	25%	16,500	225,000	Critical for effective public health response
5	Increased risk patients: Ages 12-23 mos., ≥65 yrs.; underlying medical conditions	Treat	85.5	1,710,000	25%	427,500	652,500	High risk for hospitalization and death
6	Outbreak response	Post Exposure Prophy.	~ 2 million	~ 40,000	2%	40,000	692,500	Treatment & prophylaxis to contacts stop outbreaks
7	HCWs in emergency departments, ICU, EMS, dialysis centers	Prophy.	1.2	240,000	x4	960,000	1,652,500	Most critical to prevent absenteeism and surge capacity response
8	Pandemic societal responders & HCWs without direct patient contact	Treat	10.2	204,000	25%	51,000	1,703,500	Impact on maintaining health, implementing pandemic response, maintaining societal functions
9	Other outpatients	Treat	180	3,600,000	25%	72,000	1,775,500	Those who develop influenza and do not fit in about groups
10	Highest risk outpatients	Prophy.	2.5	50,000	x4	200,000	1,975,500	Prevents illness in highest risk groups
11	Other HCWs with direct patient contact	Prophy.	8.0	160,000	x4	640,000	2,615,500	Reduce absenteeism and preserve optimal health care response

Note: This does not include calculations for family members of high priority or high-risk individuals

Appendix 1.
Assumptions, Definitions, and Abbreviations

Assumptions:

- US population as per estimated population in table = 314.4 million
- AZ population in 2004 = 5,832,150 (2004)
- Therefore, AZ/US Ratio ~ 2%

C.F.=Conversion Factors: Mirroring assumptions in HHS PIP 11-05 document for US

- 75% of hospitalized patients would get treated.
- 25% of select priority groups would get infected and need treatment.
- Two million people in the US may need Post Exposure Prophylaxis (PEP); 2% of that = 40,000.
- x4 derives from the average need for prophylaxis for select priority groups would be the equivalent of 4 treatment courses (20 days or forty 75 mg pills)

HCWs=Health Care Workers
EMS=Emergency Medical Service providers
ICU= Intensive care units
Prophy.=Prophylaxis
NA=Not applicable
Treatment Courses: 10 pills (i.e. Five days of 75 mg pills twice a day)
Public Health Responders (PHR): Public health, vaccinators, vaccine and antiviral manufacturers
Public safety: Police, fire, corrections
Outbreak response: (Nursing homes and residential settings)

Source of US population and suggested priority groups: U.S. Department of Health and Human Services' HHS Pandemic Influenza Plan, November 2005. Appendix D: NVAC/ACIP recommendations for prioritization of pandemic influenza vaccine and NVAC recommendations on pandemic antiviral drug use, table D-2, page D-21.
http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf

Arizonans who would receive Antivirals Based on Appendix 1's priority Groups and Estimates:	#	% of population
Treatment	775,500	13.2%
Prophylaxis	490,000	8.5%
Treatment or Prophylaxis	1,265,500	21.7%

Supporting documents:

1. HHS Pandemic Influenza Plan, November 2005. U.S. Department of Health and Human Services. http://www.hhs.gov/pandemicflu/plan
2. HHS Pandemic Influenza Plan, Part 1--HHS Strategic Plan, Appendix D: NVAC/ACIP Recommendations on Use of Vaccines and NVAC Recommendations on Pandemic Antiviral Drug Use. http://www.hhs.gov/pandemicflu/plan/pdf/AppD.pdf
3. HHS Pandemic Influenza Plan, Part 2—Public Health Guidance for State and Local Partners, Supplement 7: Antiviral Distribution and Use. http://www.hhs.gov/pandemicflu/plan/pdf/S07.pdf

Arizona Department of Health Services

Clinician Fact Sheet: Antivirals for Influenza 2005-2006

Four antiviral drugs are licensed for treatment and chemoprophylaxis

- Antivirals shorten the course of illness when given within the first 1-2 days of influenza symptoms
- Avoid antivirals in pregnant women unless benefit outweighs risk
- Though usually effective for influenza A, this season amantadine and rimantadine are not recommended in the U.S. due to high levels of resistance

	Amantadine (Symmetrel®)	**Rimantadine** (Flumadine®)	**Oseltamivir** (Tamiflu®)	**Zanamivir** (Relenza®)
Effective for Flu A	**Not recommended for 2005-2006 season**		**Yes**	**Yes**
Effective for Flu B	**No**	**No**	**Yes**	**Yes**
Mode	**Oral**	**Oral**	**Oral**	**Inhaled**
Treatment	**≥ 1 y.o.**	**≥ 13 y.o.**	**≥ 1 y.o.**	**≥ 7 y.o.**
Prophylaxis	**≥ 1 y.o.**	**≥ 1 y.o.**	**≥ 1 y.o.**	**N/A**

Priority groups for treatment with antiviral medicines

- Any person with a potentially life-threatening influenza-related illness
- Any person at high risk for serious complications of influenza and who is within the first 2 days of illness onset

Priority groups for chemoprophylaxis with antiviral medicines

- All residents and workers during an institutional outbreak
- All persons at high risk of serious influenza complications if they are exposed to a known or suspected case of influenza

Consider antiviral use in these patients if local supplies are adequate:

Chemoprophylaxis

- Persons in communities where influenza viruses are circulating (influenza outbreak usually lasts 6-8 weeks)
- Persons at high risk of serious complications who cannot get vaccinated.
  Persons at high risk of serious complications who have been vaccinated but have not had time to mount an immune response to the vaccine. In adults, chemoprophylaxis should occur for 2 weeks after vaccination.
- Persons with immunosuppressive conditions who are not expected to mount an adequate antibody response to influenza vaccine.
- Heath-care workers with direct patient care responsibilities who have not been vaccinated

Treatment

- Infected adults and children aged ≥1 year who do not have conditions placing them at high risk for serious complications secondary to influenza infection.

Length of Antiviral Treatment and Chemoprophylaxis

	Treatment Length	**Chemoprophylaxis Length**		
		After exposure	Institutional outbreak	After vaccine**
Amantadine	3-5 days*	7 days	Until outbreak over	2 weeks
Rimantadine				
Oseltamivir	5 days	7 days	Until outbreak over	2 weeks
Zanamivir		N/A	N/A	N/A

*Until afebrile 1-2 days ** If antiviral prophylaxis is desired for high-risk individuals during the time immunity is developing

Pediatric Points

- Children ≤ 9 years old who have never had an influenza vaccine need 2 doses of influenza vaccine, ≥ 1 month apart to be optimally protected. Therefore, if a high-risk child is vaccinated when there is influenza in the community, antiviral prophylaxis may need to be continued for 6 weeks for optimal protection.
- For pediatric antiviral use where no liquid formulation is available, open the capsule or crush the tablet, and give the appropriate dose in cherry syrup.

ANTIVIRAL MEDICINES

Amantadine [100 mg capsule; 50 mg/5 ml syrup]

- Treatment and prophylaxis (T&P) of influenza A in ≥ 12 months of age.
- Standard dose in adults for both T&P: 100 mg PO twice a day.
- Standard dose in children for T&P: 5 mg/kg/day PO in two divided doses (max of 150 mg/day).
- Side effects: CNS effects (e.g. trouble concentrating, insomnia & lowered seizure threshold, dry mouth, urinary retention).
- Decrease dose to 100 mg Q day
    - CrCl ≤ 50 ml/min
    - Age ≥ 65 years
    - When side effects occur on 100 mg BID

Rimantadine [100 mg tablet; 50 mg/5 ml syrup]

- Treatment of influenza A in ≥ 13 y.o.
- Prophylaxis of influenza A in ≥ 1 y.o.
- Standard dose in adults: 100 mg PO twice a day (see above table for length)
- Standard dose in children: 5 mg/kg/day PO in two divided doses (max of 150 mg/day).
- Similar but fewer side effects than amantadine
- Decrease dose to 100 mg Q day
    - Nursing home residents
    - Age ≥ 65 years
    - Severe hepatic dysfunction
    - CrCl ≤ 10 ml/min
    - When side effects occur on 100 mg BID

Oseltamivir (Tamiflu®) [75 mg tablet; 60 mg/5 ml suspension]

- Treatment and prophylaxis of influenza A & B in ≥ 12 months old.
- Treatment: 75 mg PO **twice daily** for 5 days.
- Lower dose in children based on weight:
  ≤ 15 kg, 30 mg BID;
  >15-23 kg, 45 mg BID;
  >23-40 kg, 60 mg BID;
  >40 kg, 75 mg PO BID.
- Prophylaxis: 75 mg PO **once daily**
- Side effects: nausea & vomiting
- Reduce dose to 75 mg every other day when CrCl 10-30 ml/min

Zanamivir (Relenza®) [Inhaler]

- Treatment of influenza A & B in ≥ 7 years of age.
- Inhalation (10 mg) twice daily for 5 days.
- Side effects: Bronchospasm

For more detailed information about each antiviral medication

See http://www.cdc.gov/flu/professionals/treatment

Updated 19 Jan 2006

Arizona Department of Health Services

Clinician Fact Sheet: Influenza 2005-2006

Epidemiology

- **Human** disease is caused by influenza A or influenza B
- Ongoing minor antigenic changes require yearly vaccination in the fall
- Knowing the currently circulating strain aids in decisions regarding antiviral treatment and prophylaxis

Clinical Presentation

- High fever, chills, prostration, muscle aches, sore throat, coryza, cough; at times, also vomiting and diarrhea

Differential Diagnosis

- Febrile respiratory illnesses such as bacterial pneumonia, mycoplasma, adenovirus, avian influenza (e.g. influenza A H5N1), and SARS

Laboratory

- Rapid testing of nasopharyngeal swabs for influenza
- Consider NP swab for respiratory viral culture (if positive, allows for further typing of isolate)
- Do not order routine viral **culture** if avian influenza is suspected

Infection control

- Droplet precautions (mask within 3-6 feet)
- Routine standard precautions and good handwashing before & after patient contact

Treatment & Prophylaxis

- Antivirals shorten the course of illness when given within the first 1-2 days of influenza symptoms
- CDC recommends against the use of amantadine & rimantadine for the 2005-2006 season

	Amantadine (Symmetrel®)	**Rimantadine** (Flumadine®)	**Oseltamivir** (Tamiflu®)	**Zanamivir** (Relenza®)
Effective for Influenza A	**Not recommended for 2005-2006 season**		**Yes**	**Yes**
Effective for Influenza B	**No**	**No**	**Yes**	**Yes**
Mode	**Oral**	**Oral**	**Oral**	**Inhaled**
Treatment	**≥ 1 y.o.**	**≥ 13 y.o.**	**≥ 1 y.o.**	**≥ 7 y.o.**
Prophylaxis	**≥ 1 y.o.**	**≥ 1 y.o.**	**≥ 1 y.o.**	**Not licensed**

Follow CDC's recommendations for ages and contraindications

- Don't use smaller doses than recommended
- Only use LAIV (Flumist™) in healthy people ages 5 years-49 years
- Persons receiving LAIV should avoid close contact with severely immunosuppresed people for 7 days
- Contraindications to inactivated influenza vaccine or LAIV
    - Anaphylactic allergy to eggs
    - Previous Guillain-Barré syndrome during the 6 weeks following a previous influenza vaccine

Remember Pneumovax® or Prevnar® pneumococcal vaccine for high-risk individuals.

Influenza Vaccine Recommendations for 2005-2006 season

Inactivated intramuscular shot [Multiple manufacturers]:

- Ages ≥ 50 y.o.
- All children ages 6 mo.-23 mo.
- Household contacts and out-of-home caretakers of infants < age 6 mo.
- Ages 2 y.o.-64 y.o. with a chronic medical conditions (e.g. heart disease, lung disease, asthma, diabetes, kidney disease, immunosuppression, etc.)
- Pregnant during influenza season.
- Children age 6 mo.-18 y.o. on chronic aspirin therapy.
- Health care workers (HCW) with direct patient care.
- Residents in nursing home or long-term care facility.
- Anyone wishing to reduce their risk of influenza.

Live attenuated influenza vaccine (LAIV) [Flumist™]:

- Healthy, nonpregnant people ages 5 y.o. through 49 y.o., including close contacts of infants and many health care workers

Pediatric pointers

- Children ages 5 years-8 years old receiving any influenza vaccine for the first time need two doses of vaccine.
    - Two inactivated shots should be spaced ≥ 4 weeks apart
    - Two LAIV doses should be separated by 6-10 weeks
- Notify local or county health department for pediatric influenza deaths.

Staphylococcal and MRSA disease associated with influenza

- MRSA is becoming a community-acquired infection
- Coagulase positive staphylococcus secondary respiratory infections are more likely with influenza
- During the 2003-2004 season, CDC reported severe illness and death associated with influenza and MRSA
- ➢ Physicians caring for patients who have influenza and worsening respiratory status requiring IV antibiotics should consider using **vancomycin** for staphylococcal coverage until culture results are available and/or clinical improvement occurs
- Many oral antibiotics do not cover MRSA
- Oral antibiotics that may be effective against MRSA
    - Trimethoprim-sulfamethoxazole
        - Poor against *Streptococcus pneumoniae*
        - Avoid in pregnancy
    - Clindamycin (Good against *Streptococcus pneumoniae*)

For More Information

- ADHS website at http://www.azdhs.gov/phs/immun/providersflu.htm
- Centers for Disease Control and Prevention website at www.cdc.gov/flu
- MMWR July 29, 2005 "Treatment and Control of Influenza" at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm
- Recorded ADHS Hotline for the Public: **Metro Phoenix** 602-364-4500
  Statewide 1-800-314-9243

Arizona Department of Health Services
Division of Public Health Services